of the description of claim 5. Accordingly, Applicants respectfully submit that the rejection under 35 U.S.C. 112, second paragraph has been overcome.

The Rejection under 35 U.S.C. 103(a) over von der Osten and Braxton

Claims 1-6, 8, 9, and 20 have been rejected under 35 U.S.C. 103(a) as being unpatentable over von der Osten et al. (US 6,300,116) and Braxton et al. (US 5,766,897). Applicants respectfully traverse this rejection as there is no motivation to combine the references, as required by MPEP 2143.01. There would be no motivation to combine von der Osten's teaching of autoproteolytic stability with Braxton's teaching of immune surveillance. Autoproteolytic stability refers to a mechanism that hinders the protease from attacking itself, while the immune surveillance technique allows the protease to go unrecognized by a mammal's immune system. The issues of autoproteolytic stability and immune surveillance are completely separate problems. Thus, von der Osten teaches protecting the protease from itself, and Braxton teaches protecting the protease from a foreign immune system. One skilled in the art would have no motivation to combine von der Osten's teachings of altering amino acids for the purpose of increasing autoproteolytic stability with Braxton's teachings of masking a polypeptide from immune surveillance. Thus, the obviousness rejection given in the Office Action does not establish a *prima facie* case of obviousness. Therefore, Applicants contend that the claimed invention is unobvious and that the rejection should be withdrawn.

The Office Action states that there is no need that the prior art supply the same motivation that Applicant had for making the product. However, Applicants contend that the prior art would not have provided one of ordinary skill in the art with any motivation to make the same product. Von der Osten teaches that making an amino acid substitution at a position corresponding to subtilisin BPN' position 134 will exhibit increased autoproteolytic stability. Thus, von der Osten teaches targeting specific positions in order to keep the protease from attacking itself. Braxton teaches increasing protein stability in mammals by substituting amino acid residues with cysteine and attaching polyethylene glycol [PEG] to the cysteine, in order to mask epitopes that may be recognized by a mammalian immune defense system. Hence, Braxton teaches random cysteine

substitutions at a polypeptide region followed by attaching PEG to the cysteine in order to protect it from immune surveillance.

While both von der Osten and Braxton teach protection of the protein, the mechanisms in achieving the protection are clearly different and would not have motivated one of ordinary skill in the art to combine the references. One skilled in the art interested in the teachings of von der Osten would be focused on protecting the protease from itself, as von der Osten provided a method of increasing autoproteolytic stability by substitutions at specific positions. Von der Osten does not teach or suggest that this method could be enhanced or applicable to any other form of protease protection. Further, von der Osten never indicates that this method is insufficient to protect the protease from itself; therefore, one skilled in the art would have no motivation to search beyond the teachings of von der Osten to find a better way to protect the protease from itself.

Therefore, Applicants contend that a *prima facie* case of obviousness has not been established, and the claimed invention is not obvious in view of the cited references.

The Rejection under 35 U.S.C. 103(a) over von der Osten, Braxton, and Powell

Claim 21 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Von der Osten et al. (US 6,300,116), Braxton et al. (US 5,766,897), and Powell et al. (US 6,060,546). Applicants respectfully traverse this rejection because there is no motivation to combine the references, as required in MPEP 2143.01.

There is no motivation to combine von der Osten, or Braxton with Powell. Powell only teaches the preparation of a personal care composition comprising subtilisin SP 544, while the other references specifically teach subtilisin modification and substitution. One skilled in the art would not be motivated to combine references teaching specific modifications or substitutions of specific regions of different subtilisins with Powell's general description of a personal care composition comprising subtilisin SP 544. Von der Osten specifically teaches altering amino acids in subtilisin 309 to inhibit proteolysis, and Braxton specifically teaches substitution of cysteine to then conjugate polymers to protect from immune surveillance. While Powell teaches that subtilisins can be used in personal care compositions, there would be no motivation to combine that broad and general teaching with references teaching inhibition of proteolysis or polymer conjugation.

Therefore, Applicants contend that a *prima facie* case of obviousness has not been established, and the claimed invention is not obvious in view of the cited references.

Conclusion

Applicants have made an earnest effort to place their application in proper form and to distinguish the invention as now claimed from the applied references. WHEREFORE, Applicants respectfully request reconsideration of this application, entry of the amendments presented herein and allowance of Claims 1-21.

Respectfully submitted,

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By _____

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

1. A protease conjugate comprising a protease moiety and one or more addition moieties wherein the protease moiety comprises a first epitope region, a second epitope region, and a third epitope region, wherein each addition moiety is covalently attached to an epitope protection position of the protease moiety, wherein:

(a) the epitope protection positions for the first epitope region are selected from the group of positions corresponding to positions consisting of 1, 2, 3, 4, 5, 6, 7, 12, 17, 36, 40, 41, 43, 44, 45, 67, 86, 87, 89, 206, 209, 210, 212, 213, 214, 215, and 216 of the amino acid sequence of subtilisin BPN' set forth in SEQ ID NO:1;

(b) the epitope protection positions for the second epitope region are selected from the group of positions corresponding to positions consisting of 25, 26, 27, 46, 47, 48, 49, 50, 51, 52, 53, 54, 91, 99, 100, 101, 102, 127, 128, 129, 130, 131, 132, 133, 134, 136, 137, 138, 140, 141, 144, and 145 of the amino acid sequence of subtilisin BPN' set forth in SEQ ID NO:1; and

(c) the epitope protection positions for the third epitope region are selected from the group of positions corresponding to positions consisting of 9, 10, 22, 23, 24, 62, 63, 143, 146, 154, 155, 156, 157, 172, 173, 187, 189, 195, 197, 203, 204, 253, 254, 256, 265, 267, 269, 271, 272, and 275 of the amino acid sequence of subtilisin BPN' set forth in SEQ ID NO:1.